CASE REPORTS

Poisoning by Organic Phosphate Insecticides

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A NINE-YEAR-OLD Japanese boy, vacationing on his grandparents' ranch, spent about one and a half hours with his grandfather and two teen-age cousins while they were dusting a strawberry patch. The dusting agent used, a 2 per cent adsorption of parathion on a wettable dust, was marketed under the trade name of "Thiondust" to be used in that concentration. It was adequately labeled in English regarding toxicity, precautions and first aid treatment. The label also included instructions for physicians. The distributor keeps on his sales counter illustrated booklets printed in nonprofessional language by the California Department of Industrial Relations containing warnings and instructions in English and Spanish.

The weather on the day the dusting was done was hot and windy. Perhaps because of language difficulties, the adults did not comprehend the dangers involved. The grandfather had a mask which he wore for a short time, then discarded as a nuisance. The nine-year-old boy did not wear a mask or protective clothing.

After the first spraying operation none of the persons concerned had any symptoms.

The second day about two hours were spent in the same manner. On the way home the boy rode alone in the load compartment of the truck with the bags of Thiondust, but it is not known whether or not he was in actual contact.

Shortly afterward, all four began to complain of headache. In the adults, the symptoms did not progress further, but the boy rapidly became acutely ill. His grandmother, at first unconcerned about the headache, soon noticed that he was perspiring profusely. She gave him an enema but before he had expelled it, he seemed to be losing consciousness and she called a physician. He was rushed to the nearest hospital, ten miles away, by ambulance.

He arrived there at 3:30 p.m. in a state of shock, vomiting frequently. The temperature was 99.2° F. The pupils were constricted. The neck was not stiff. Respirations were rapid and difficult. There were no rales. The heart rate was rapid and regular and no murmurs were heard. There were no abnormalities in the abdomen and genitalia. The extremities were cold and sweaty.

Given 0.3 mg. of atropine intravenously immediately on arrival, the patient responded quickly. At 4 p.m. the pupils were dilated and the patient was able to talk intelligently and seemed much better. At 4:30 p.m. he passed a large liquid stool involuntarily and seemed incoherent. The nurse's notes indicate that the pulse was rapid and that there was "mucus in throat." At 4:40 p.m. the nurse wrote, "pupils contracted, eyes twitching, not responding." At 4:50 he was given 0.3 mg. of atropine again but did not respond as previously. Muscle twitching became generalized and the patient was soon in a state of unremitting convulsions. He was given 0.4 mg. of atropine by vein twice more, but with no apparent effect. The pupils remained pinpoint and he was mildly cyanotic, in spite of oxygen by nasal catheter and postural drainage.

At about 8 p.m. voluntary respirations ceased rather abruptly. Artificial respiration and respiratory and cardiac stimulants were used but at 9:05 no heart action could be found and the patient was pronounced dead.

Blood had been taken for routine laboratory examination, and the report on it was: Hemoglobin content, 15.4 gm. per 100 cc.; erythrocytes, 5,290,000 per cu. mm.; leukocytes, 29,900 per cu. mm.—28 per cent stabs, 62 per cent segmented, 9 per cent lymphocytes and 1 per cent monocytes.

At autopsy the following conditions were noted: Congestion and edema of the lungs; subepicardial and subpleural petechiae; postmortem fluidity of the blood; focal atelectasis of the lungs; congestion of the liver, spleen, and kidneys. The pathologist said that the findings are consistent with death by asphyxia resulting from exposure to a chemical agent.

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CASE REPORT NO. 2

The person concerned in the following report was not seen by a physician. The information given here was obtained from the Coroner of Santa Cruz County and the California State Department of Industrial Relations.

A 35-year-old pilot of a crop dusting plane carrying "Vaportone," a powder containing 1.5 per cent tetraethylpyrophosphate (TEPP) was doused with the powder from head to foot when the dust bin flew open at a crash landing after gradual loss of

altitude short of the destination. As he crawled out of the open cockpit he refused help from persons who went to his aid, said he was not injured and would not permit them to call an ambulance. He asked for water, drank it, and then immediately complained of illness and asked for a physician. A moment later he slumped to the ground. He died in a very few minutes.

At autopsy, the only finding of significance was that the respiratory passages were thickly coated with the dust. There were no fractures. The cervical spine was especially examined and found intact. The only evidences of injury were a few superficial abrasions.

An ambulance driver, a mortician and a pathologist all complained of headache and stomach cramps after handling the body.

The Civil Aeronautics Authority found no evidence that the accident had been the result of mechanical failure. Investigators later learned that the pilot had been known to spray the dust over workers when they had not gotten off the field in time. He had been warned against this practice by the California State Department of Industrial Relations. For a few days before the accident he had complained of headache and visual troubles. His employer had urged him to have a blood test but he had refused.

DISCUSSION

The organic phosphate insecticides were developed during the last war by German chemists incidental to a search for war gases. Although at first used only for larger agricultural units, they are now available in small quantities in many garden supply stores and have created a growing public health problem.

The California State Department of Public Health reported 158 occupationally incurred cases of organic phosphate poisoning in 1953—128 of them from parathion. There were five known fatalities. It is probable there were many other cases not reported.

The organic phosphate insecticides now in common use in California are TEPP, parathion (diethyl-p-nitrophenyl thiophosphate), Demeton or Systox (diethoxy thiophosphoric ester of 2 ethyl mercapto ethanol) and Malethion (dimethoxy dithiophosphate of diethyl mercapto succinate).

In pure form they are amber to straw-colored oily liquids, stable at room temperatures.[16] Parathion hydrolyzes very slowly and has a higher degree of solubility in lipids than do the other preparations.[10] These properties, which make it the most dangerous of the group, have also led to its acceptance as the insecticide of choice for most crops. Demeton is a "systemic" insecticide. As it will control pests in all parts of the plants when applied to any one part, it is of obvious value in inedible crops and its use has so far been restricted to cotton. Malethion is the least toxic of the group mentioned.

These compounds are readily absorbed from skin or mucous membranes and are toxic by contact, inhalation, ingestion or injection. Their toxic effect is due to their ability to inactivate cholinesterase. Acetyl choline serves as a chemical mediator for the nerve impulse at parasympathetic synapses. It is normally destroyed within one hundredth of a second by cholinesterase. As a result of this inhibition, acetyl choline accumulates in the tissues, producing effects resembling those of prolonged stimulation of cholinergic nerves.

The effect of a single dose of TEPP and parathion is partly reversible for the first several hours. Repeated doses produce a progressive and largely irreversible inactivation of cholinesterase.[6] Plasma cholinesterase is restored, presumably by the liver, at the rate of approximately 14 per cent of original activity on the first day, 9 per cent on the second day and 2 to 6 per cent on subsequent days until normal levels are restored in about three weeks. Restoration of erythrocyte and tissue activity parallels the rate of erythrocyte replacement and requires about three months (1 per cent per day).[11]

After absorption, the plasma cholinesterase may fall to nearly zero and that of the erythrocytes to below 10 per cent of normal activity before symptoms appear. Symptoms may disappear as the erythrocyte activity increases above 15 per cent of normal.[12] Thus, repeated exposures may lower cholinesterase levels to a dangerous point without producing symptoms; then a subsequent, perhaps mild, exposure may be fatal.

The effects of acetyl choline are called *muscarinic* when the site of action is at glands and smooth muscle and *nicotinic* when it is at ganglia, skeletal muscle and the central nervous system. The earliest muscarinic effects are anorexia and nausea, which may be aggravated by smoking. Soon afterward vomiting, abdominal cramps and excessive perspiration and salivation may occur. Heavy exposure will cause diarrhea, tenesmus and incontinence. The blood pressure tends to rise, the pupils to constrict; and increased bronchial secretion leads to pulmonary edema and cyanosis.

The nicotine-like effects manifest themselves shortly after the onset of nausea and vomiting. At first, fasciculations of the eyelids and tongue are seen. These spread to involve the muscles of the face and neck and become generalized. Extraocular muscle involvement may cause nystagmus.

The earliest central nervous system effects are giddiness, restlessness and anxiety and may be noted even before the onset of nausea and vomiting. Headache and insomnia follow. Severe exposure causes ataxia, disorientation, drowsiness and slurring speech. Coma precedes death.[8]

The muscarinic symptoms are first to appear and they respond readily to moderate doses of atropine. The later occurring nicotinic effects require much larger doses for control.

These facts have led to an unfortunate sequence of events which is well illustrated in many of the published case reports[1, 2, 8, 9, 12] and by the case

here reported. The patient is first seen with nausea, vomiting, excessive perspiration and salivation, and miosis. He is given a "safe" dose of atropine and in a few minutes he is better. The pupils have dilated and the excessive flow of secretions has been relieved. A short time later, however, the more dangerous nicotinic and central nervous system effects come into play and unless treatment is prompt and vigorous the patient is soon dead.

The acute emergency lasts from 24 to 48 hours and the patient must be closely watched.

Atropine is the only known specific medication. It is very effective against the muscarinic effects, but much less so against the nicotinic and central nervous system effects. It can be used in dosage which would be dangerous were it not for the fact that a physiological antagonist is already present in the tissues in relatively large quantities. Two milligrams should be administered when the patient is first seen and this dose should be repeated at least every 15 minutes until atropine effects are noted. It would seem safe to say that as long as the pupils are miotic the patient has not received enough atropine. The only seriously poisoned persons who have survived have received large doses, and in none of the fatal cases thus far reported were such doses given. One patient who lived received 14.2 mg. in the first two hours and ten minutes.[15]

Since peripheral respiratory failure precedes cardiac failure, life can be prolonged and chances of survival enhanced by the use of artificial respiration when indicated. Oxygen should be administered if cyanosis occurs and a clear airway should be maintained by means such as postural drainage or suction. Although bronchiolar spasm also plays a part in respiratory failure, tracheotomy should be done if cyanosis does not disappear in response to these measures. The use of a positive pressure apparatus such as the Bennett machine may be lifesaving. Du Bois demonstrated that animals can be protected against anticholinesterase drugs by atropine. The degree of protection is greatly increased if the animals are also kept under artificial respiration. "Almost indefinite amounts of parathion up to 140 mg. per kg. of body weight were given in divided doses without visible effects to the animal," Du Bois said. He also observed that with doses beyond those required to cause respiratory failure, pronounced bradycardia developed, "the tracing showing a greatly exaggerated pulse pressure suggesting A.V. block."[4] This suggests a possible clinical value in the prophylactic use of Isuprel® (isopropylarterenol) in cases of severe poisoning and a possible danger in the use of digitalis.

Removal of clothing and careful cleansing of the entire skin surfaces should be carried out as soon as the urgent, life-saving measures have been done. Since parathion is hydrolyzed more rapidly by alkali, the use of soapy water with added soda is recommended. If there is any question concerning the possibility of ingestion, gastric lavage should also be done.

It is not safe to administer atropine to an exposed symptomatic patient and allow him to go home unless he can be carefully observed for the duration of the danger period.

Deichman found Buscopan® somewhat more effective than atropine in treating organic phosphate poisoning in rats.[3] So far as could be determined there are no reports of its use in humans.

Johns and co-workers[14] demonstrated that the convulsant effects of theophylline, theophylline-ethylene-diamine (aminophyllin), and chlorotheophylline are increased six-fold by the anticholinesterase drugs. Therefore, use of them should be avoided. Morphine is also contraindicated, for obvious reasons.

Deaths have been reported from contact with parathion in all phases of its manufacture, preparation and field use. The need for protective clothing and masks by workers concerned and the immediate and careful washing of any areas of contact is obvious. The U. S. Department of Agriculture has issued bulletins containing recommendations as to types of protective clothing and respirators. Careful instruction concerning the dangers involved and methods of protection is mandatory. The distributor ought to assume the responsibility of making certain that purchasers who know only a foreign language, are fully cognizant of these facts.

For reasons previously mentioned, a person who is exposed sufficiently to cause symptoms must avoid further exposure to any organic phosphate until the cholinesterase level returns to what is normal for the individual (or levels off if preexposure level is not known). Three weeks is a practical interval where cholinesterase determinations are not available.

The condition is recognizable even without a history of exposure. A combination of miosis with perspiration and excessive bronchial and salivary secretions should suggest it. Blood cholinesterase determinations are useful not only in diagnosis but as a guide to the degree of exposure in handlers. More recently a method for the detection of p-nitrophenol, an end-product in the metabolism of parathion, has been developed and may replace the slower cholinesterase determinations in diagnosis of poisoning by parathion.[18]

Moderate leukocytosis (15,000 to 20,000 leukocytes per cu. mm.) has been a common finding.[8]

The toxic or fatal dose is related to the size of the individual. A child may die from an exposure that will not produce symptoms in an adult. Experiments with rats have demonstrated a far greater susceptibility to the effects of di-isopropyl fluorophosphate in the infant of the species, supposedly due to lower brain cholinesterase.[7] Chamberlin and Cooke[2] reported a five-month-old infant who became seriously ill three and one-half days after the room in which his diapers had been hanging in an open cloth bag was sprayed by a parathion preparation. Children should never be allowed in the vicinity of spraying operations, and these preparations should never be used as insecticides in the home.

The authors know of no reports of ill effects from marketed foods which in California are checked for residues at the wholesale level by the State Department of Agriculture.

Pilots using these products in dusting operations are doubly endangered. The hoppers into which the dust is loaded are usually located in front of the cockpit. If the hopper is not properly sealed, the pilot may have great exposure in a short time. A dosage which would not otherwise be fatal may cause a pilot to lose control and crash his plane.[13, 19]

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